Diabetes Care
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The Effect of Substituting Water for Artificially Sweetened Beverages on Glycemic and Weight Measures in People With Type 2 Diabetes: The Study of Drinks With Artificial Sweeteners (SODAS), a Randomized Trial

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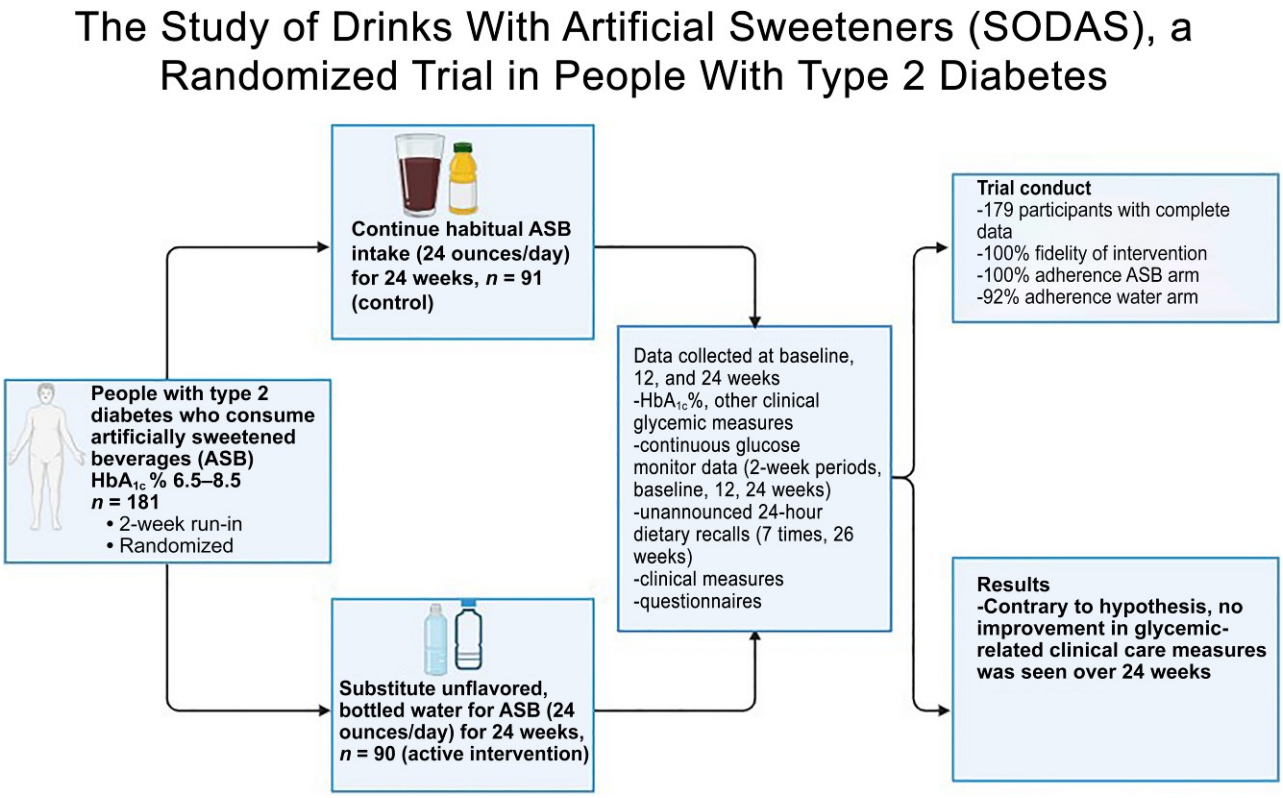
Diabetes Care 2026;49(2):239–246 | *https://doi.org/10.2337/dc25-1516*


The Study of Drinks With Artificial Sweeteners (SODAS), a Randomized Trial in People With Type 2 Diabetes
People with type 2 diabetes who consume artificially sweetened beverages (ASB)
HbA1c % 6.5–8.5
n = 181
• 2-week run-in
• Randomized
Continue habitual ASB intake (24 ounces/day) for 24 weeks, n = 91 (control)
Substitute unflavored, bottled water for ASB (24 ounces/day) for 24 weeks, n = 90 (active intervention)
Data collected at baseline, 12, and 24 weeks
-HbA1c%, other clinical glycemic measures
-continuous glucose monitor data (2-week periods, baseline, 12, 24 weeks)
-unannounced 24-hour dietary recalls (7 times, 26 weeks)
-clinical measures
-questionnaires
Trial conduct
-179 participants with complete data
-100% fidelity of intervention
-100% adherence ASB arm
-92% adherence water arm
Results
-Contrary to hypothesis, no improvement in glycemic-related clinical care measures was seen over 24 weeks

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Little evidence informs whether habitual intake of artificially sweetened beverages (ASB) affects diabetes control in people with type 2 diabetes (T2D).
- **What is the specific question we wanted to answer?**
  What is the effect of substituting plain water (the ideal standard) for habitual ASB intake in people with T2D on primary measures of diabetes control?
- **What did we find?**
  This trial provided no evidence that substituting water would improve glycemic-related clinical care measures over 24 weeks.
- **What are the implications of our findings?**
  There was no benefit to substituting water for ASBs in people with T2D who regularly consume ASBs. If anything, the results suggest maintaining usual ASB intake may be a tool to manage T2D if glycemic measures are controlled and stable.

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The Effect of Substituting Water for Artificially Sweetened Beverages on Glycemic and Weight Measures in People With Type 2 Diabetes: The Study of Drinks With Artificial Sweeteners (SODAS), a Randomized Trial

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Diabetes Care 2026;49:239–246 | https://doi.org/10.2337/dc25-1516

ORIGINAL ARTICLE

OBJECTIVE

To test the effect of substituting plain water (the ideal standard) for habitual artificial sweetened beverage (ASB) intake by people with type 2 diabetes (T2D) on primary measures of diabetes control.

RESEARCH DESIGN AND METHODS

The Study of Drinks with Artificial Sweeteners in People with T2D (SODAS) was conducted at two academic health centers and was a randomized, two-arm, parallel trial with a 2-week run-in period and a 24-week active intervention period. Adults with T2D (*n* = 181; HbA_{1c} 6.5–8.5%; aged ≥35 years) who regularly consumed commercial ASBs were randomized to receive and consume 24 oz daily for 24 weeks of either *1*) a commercial ASB of choice (control) or *2*) an unflavored, sparkling or still, bottled or canned water of choice in place of ASBs. The outcomes measures were collected at baseline, 12, and 24 weeks and included the primary measure (HbA_{1c}) and related secondary measures (fructosamine, fasting glucose and insulin, body weight, and continuous glucose monitor metrics).

RESULTS

A total of 179 participants provided complete data over 24 weeks. From baseline to 24 weeks, the mean difference in change of HbA_{1c} was 0.29% (SE 0.12; *P* = 0.013) higher in the water arm compared with the ASB arm. There were no significant effects on secondary clinical measures, but data were directionally consistent with the primary results.

CONCLUSIONS

For people with T2D and HbA_{1c} <8.5% who regularly consume ASBs, this trial provided no evidence that substituting water would improve glycemic-related clinical care measures over 24 weeks.

The global prevalence of adults with diabetes is ∼537 million. More than 38 million people in the U.S. have diabetes, with 90–95% of adults with diabetes having type 2

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Received 24 June 2025 and accepted 17 September 2025

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Clinical trial reg. no. NCT03944616, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.30559481.

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diabetes (T2D) (1,2). The complexity of managing T2D requires an integrated, evidence-based strategy, due to myriad complications and comorbid conditions being strongly linked to hyperglycemia and glycemic patterns (3,4). Although managing glycemia in T2D is primarily achieved through pharmacotherapy, the integrated approach emphasizes the importance of health-related behaviors, particularly nutritional therapy and dietary recommendations (5–7).

A specific avenue for dietary recommendations that is of high importance and interest to people with T2D but that is lacking direct scientific evidence is how the use of artificial sweeteners (AS) affects clinical measures of diabetes control and underlying mechanisms that, in turn, may affect clinical phenotypes (5,6,8). The vast majority of AS intake in the U.S. diet occurs via artificially sweetened beverages (ASBs), defined as zero-calorie (or near zero) beverages sweetened with Food and Drug Administration–approved artificial sweeteners. People with diabetes are the highest consumers of ASBs, tending to consume them as a replacement for dietary sources of sugar, especially in place of sugar-sweetened beverages (8–12). This is the intended use of ASBs and has been endorsed by clinical and scientific organizations, whereas water consumption is considered the ideal standard in dietary recommendations (6,8). The clinical and public health concern is that there are few data to support or refute the benefit or harm of habitual ASB consumption by people with T2D, and the related evidence in people without diabetes suggests ASBs may affect T2D risk and glycemic measures in a negative manner (13–15).

To address this gap and directly inform standard-of-care guidelines and a specific medical nutritional therapy question for people with T2D, we conducted a randomized parallel trial to test the effect of substituting plain water (the ideal standard) for habitual ASB intake in people with T2D on primary measures of diabetes control. Based on the evidence and dietary recommendations, we hypothesized that consuming water in place of ASBs would reduce HbA_{1c} and other glycemia-related measures in people with T2D.

RESEARCH DESIGN AND METHODS

The Study of Drinks with Artificial Sweeteners in People With Type 2 Diabetes (SODAS) was a two-site, two-arm, parallel trial with a run-in period of 2 weeks and an active intervention period of 24 weeks that randomized 181 adults with T2D (HbA_{1c} 6.5–8.5%), aged 35 years or older, who were usual consumers of commercial ASBs to receive and consume 24 oz daily of either *1*) a commercial ASB of choice; or *2*) an unflavored, sparkling or still, bottled or canned water of choice in place of ASBs.

Participants

The trial was conducted at the University of California, Irvine, and the University of Minnesota, Minneapolis, between June 2019 and March 2023. The study included adults with T2D who were able to provide informed consent and who met the criteria described in Supplementary Methods.

The trial was performed according to the principles of the Declaration of Helsinki, in accordance with the Medical Research Involving Human Subjects Act and the standards of Good Clinical Practice. The institutional review board of the University of California, Irvine, approved the protocol and amendments on 24 January 2019. The study was registered at ClinicalTrials.gov (identifier NCT03944616) prior to initiation; the protocol and statistical analysis plan are published there. Informed written consent was obtained from all participants before enrollment. There was no participant or public involvement in the design, conduct, and reporting of the trial.

Experimental Protocol

Eligible and interested individuals were invited to enroll in a 2-week run-in period before randomization to strengthen and increase the level of scientific inference for the trial. During the run-in period, participants provided dietary intake data through two, unannounced 24-h dietary recalls; wore both a blinded continuous glucose monitor (CGM) (Abbott Freestyle Libre) and a blinded objective physical activity and sleep monitor (activPAL) to assess both usual glycemic excursions essential to study aims and usual activity and sleep habits; and provided a gut microbiome sample for storage for future analyses. Participants who successfully completed the run-in period and were interested in participating in the full intervention were randomly assigned in a 1:1 ratio to the control group (continue habitual intake of commercial ASBs, 24 oz/day) or the intervention group (unflavored, sparkling or still, bottled or canned water of choice in place of ASBs, 24 oz/day). Randomization was performed with the use of permuted blocks and was stratified by site and sex. The randomization list was created before the start of the study and maintained by an independent statistician during the conduct of the study. The randomization list was not accessible to any other research team members.

Intervention

The intervention was the substitution of the ideal beverage per standard of care and dietary guidelines (i.e., unflavored, still or sparkling, bottled water) for ASBs. Participants were randomized to receive three daily servings (8-oz each, 24-oz total/day) of an ASB or water (unflavored, sparkling or still, bottled or canned water) of choice during the 24-week intervention period. The participants were instructed to consume the 24 oz of beverages provided each day during the intervention period, though they were allowed to consume higher volumes of ASBs if they were randomized to that arm. All participants were allowed to consume water ad hoc. Participants randomized to ASBs had their choice of commercial ASBs and whether the beverages were caffeinated. Participants randomized to water were instructed to avoid intake of ASBs and were provided with bottled or canned water to enhance adherence. If they had previously consumed caffeinated ASBs for reasons related to caffeine ingestion (e.g., alertness), they were counseled about sources of caffeine that are noncaloric and allowed to be consumed per study protocol (e.g., unsweetened teas and coffee), and/or provided caffeinated water or caffeine pills, whatever their preference, to enable optimal participation fidelity and provide them with similar levels of caffeine intake.

The intervention dose of 24-oz/day study beverages was selected because this amount represents the upper portion of usual intake by habitual consumers of ASBs (8,10–12,16). Furthermore, this level of intake aligns with the best methods for study design of interventions investigating the effects of diet where it is necessary to have a moderately large variation of intake by participants to detect an effect within a designated period (17).

The protocols for each arm were identical, except for the intervention beverage (water versus ASB). There was no other dietary counsel or advice provided and no specific instructions on when the beverages were to be consumed, because it was presumed this consideration was immaterial in relation to the primary outcome over 24 weeks, and the intervention was designed to maximize adherence. All beverages for were provided to study participants via home delivery. Details on adherence are reported in Supplementary Methods.

Outcomes

Blood-based Outcomes

Primary and secondary outcome measures were collected under fasting conditions at baseline, 12 weeks, and 24 weeks in the morning after an overnight (>10 h) fast. Clinical personnel performing measurements were blinded to intervention allocation, as were the laboratory personnel performing the specimen analyses. All analyses were performed in batch at the Advanced Research and Diagnostic Laboratory, a fully accredited central biochemistry laboratory at the University of Minnesota.

CGM and Weight Outcomes

Participants wore a blinded Freestyle Libre Pro sensor (Abbott, Chicago, IL), for three, 14-day periods (run-in, intervention weeks 11 and 12, and intervention weeks 23 and 24). At the beginning of each defined period, a sensor was placed on the underside of the participant's upper arm by the clinical research coordinator. The sensor records glucose levels every 15 min and the following metrics were calculated and reported: *1*) time in range (TIR) (the amount of time glucose readings were within a glucose range of 70–180 mg/dL [3.9–10.0 mmol/L]); this is a primary CGM metric (a difference of ≥3% [absolute percentage points] in TIR is considered clinically meaningful for a treatment group difference in mean TIR) (18). *2*) time below range (the percentage of time glucose readings were <70 mg/dL [<3.9 mmol/L]); *3*) time above range (the percentage of time glucose readings were >180 mg/dL [10.0 mmol/L]); *4*) mean glucose (mean glucose concentration during the wear period); and *5*) the SD of mean glucose values (a measure of dynamic glucose variability). Body weight was measured to the nearest 0.1 kg with a daily calibrated digital scale when participants were in a fasting state. Participants wore a gown or light clothing and no shoes.

Medication Effect Score

At each study visit, from the run-in period to the completion of the study, participants reported their prescribed pharmacotherapy regimen for glycemia. The medication effect score (MES) of a particular drug dose reflects the decrease in HbA_{1c} that is expected when that specific drug dose is used as monotherapy and is a valid and appropriate measure of diabetes regimen intensity in clinical settings and research (19) (details in Supplementary Methods). The MES was an analytic covariate and a predefined secondary end point representing diabetes regimen intensity.

Statistical Analysis

The primary outcome measure was the between-group difference in HbA_{1c} change over the 24-week intervention. Secondary outcomes were also analyzed comparing change over time between the two arms. The power estimates were based on detecting a clinically significant 0.3% difference in HbA_{1c} percentage units using a superiority framework for comparisons. We assumed the SD of HbA_{1c} to be 1.0%. We set power to 80% and the two-tailed α-level to 0.05 and planned for a repeated measures regression model (0, 12, and 24 weeks) testing the between-arm intervention effect on HbA_{1c} change over 24 weeks (treatment × time interaction), with the baseline to 24-week HbA_{1c} correlation estimated at $r = 0.8$. These assumptions provided an estimated sample size requirement of 160 participants completing the study. We designed the study for an anticipated participant attrition rate of 20% and aimed to randomize 100 participants to each intervention ($n = 200$ total) to achieve ≥80% power or higher for the primary aim. Overall, we randomized 181 participants, and 179 participants provided complete data on all measures.

The main analyses for all primary and secondary outcomes were conducted on an intention-to-treat basis, using all randomized participants. The data were analyzed using linear mixed models, with randomization group, categorical time points, and the interaction between randomization group and time, to estimate the difference between mean outcome levels in the intervention and control arms over the 24-week intervention, adjusted for sex, study site, and MES. The analysis included the 0-, 12-, and 24-week measurements available for all the participants and included random effects for individuals to account for intraclass correlation between measurements from the same person at different follow-up times. We carried out per-protocol analyses, along with prespecified sensitivity analyses that excluded participants receiving insulin therapy, stratified by sex, and further adjusted for caffeine intake (estimated via five additional, unannounced 24-h dietary recalls completed over 24 weeks), duration of T2D, type of sweeteners in ASBs consumed, and COVID-19 infection during the intervention. The statistician conducting the analyses was independent of the study and blinded to the intervention allocation. All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was set at $P < 0.05$, using two-tailed tests.

Data and Resource Availability

After publication of the main project's aims, and secondary projects using the data are complete, the data will be available through request from the corresponding author. Statistical code is available upon request.

RESULTS

Participant Characteristics

Between June 2019 and March 2023, 1,298 people were screened. Of these, 941 people did not meet all inclusion criteria, and 176 declined to participate. As seen in Fig. 1, the remaining 181 participants with T2D were randomized to one of the two conditions: ASB ($n = 91$) or water ($n = 90$). The two groups were similar with respect to baseline characteristics (Table 1); the mean age (SD) was 60.1 (10.2) years; just over half (52%) were women; and the mean HbA_{1c} (SD) was 7.19% (0.65). There were no adverse events or other unintended effects of trial interventions or trial conduct on any participant-reported outcomes. There was complete fidelity of the intervention (i.e., each participant received the home delivery of beverages aligned with the intervention arm to which they were randomized). And of the 91 participants randomized to the ASB group, there was complete

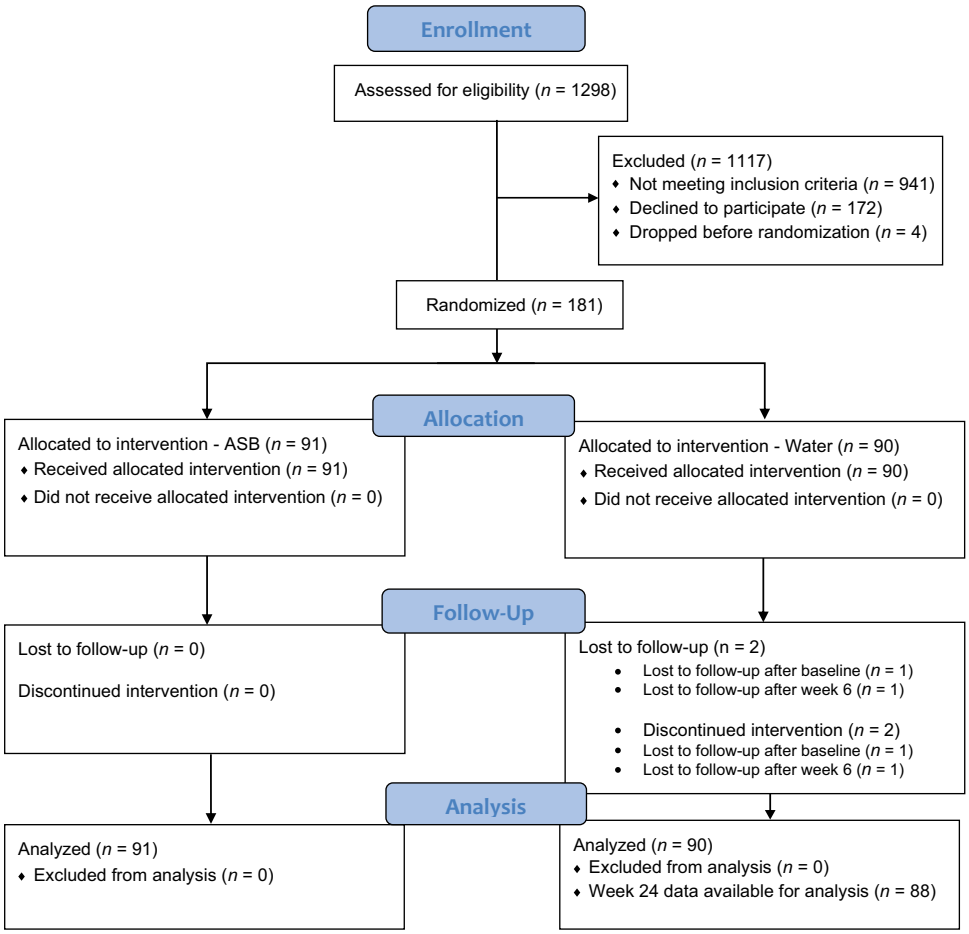
Enrollment
Assessed for eligibility (n = 1298)
Excluded (n = 1117)
Not meeting inclusion criteria (n = 941)
Declined to participate (n = 172)
Dropped before randomization (n = 4)
Randomized (n = 181)
Allocation
Allocated to intervention - ASB (n = 91)
Received allocated intervention (n = 91)
Did not receive allocated intervention (n = 0)
Allocated to intervention - Water (n = 90)
Received allocated intervention (n = 90)
Did not receive allocated intervention (n = 0)
Follow-Up
Lost to follow-up (n = 0)
Discontinued intervention (n = 0)
Lost to follow-up (n = 2)
Lost to follow-up after baseline (n = 1)
Lost to follow-up after week 6 (n = 1)
Discontinued intervention (n = 2)
Lost to follow-up after baseline (n = 1)
Lost to follow-up after week 6 (n = 1)
Analysis
Analyzed (n = 91)
Excluded from analysis (n = 0)
Analyzed (n = 90)
Excluded from analysis (n = 0)
Week 24 data available for analysis (n = 88)

Figure 1—SODAS trial flow diagram.

self-reported adherence by participants (participants reported consuming 94.5% of provided ASBs on average), and all 91 participants provided complete data. Of the 90 participants randomized to drink water, 83 reported being >90% adherent over the 24-week intervention, and 88 participants provided full data.

Outcomes

Primary Outcome

From baseline to 24 weeks, the mean HbA_{1c} decreased from 7.19% to 7.14% in the ASB arm and increased from 7.20% to 7.44% in the water arm, for a mean difference in change of 0.29% (SE 0.12; P = 0.013) higher in the water arm (Table 2).

Secondary Glycemic and Weight Outcomes

The intervention effects on secondary glycemic and weight outcomes are also listed in Table 2. From baseline to 24 weeks, the mean fructosamine level (µmol/L) did not change in the ASB arm and increased in the water arm, with a mean difference in change of 6.22 µmol/L higher in the water arm (SE 4.92; P = 0.21). The mean fasting glucose level increased from 147.5 to 149.2 mg/dL in the ASB arm and increased in the water arm from 147.6 to 153.7 mg/dL, resulting in a mean difference in change of 4.71 mg/dL higher in the water arm (SE 6.43; P = 0.47). The mean fasting insulin levels had a mean difference in change of 11.8 pmol/L higher in the ASB arm compared with the water arm (SE 13.4; P = 0.38). Mean weight (kg) was stable in the water arm, whereas there was a modest decrease in the ASB arm; the mean difference in change estimated in the model was 1.11 kg higher in the water arm (SE 0.55; P = 0.045).

To provide context for the primary and main secondary end points in the trial, we also report the formal main analysis of the MES score (predefined secondary end point for change in diabetes regimen intensity). Over 24 weeks, the MES score for participants randomized to ASBs stayed stable at 1.60, and the MES score for participants randomized to the water arm did not change materially (1.97 at baseline to 1.92 at week 24). In the analytically adjusted model, there was a −0.06 lower MES after 24 weeks in those randomized to the water arm compared with those randomized to the ASB arm (P = 0.32).

CGM Outcomes

The primary CGM metric was percent TIR, and this decreased in both arms over the 24 weeks. However, there was a 3.6% greater reduction (SE 3.0; P = 0.29) in the water arm compared with the ASB arm over time. Time above range and mean glucose levels increased in both arms over time, but the change was greater, though nonsignificant, in the water arm compared with the ASB arm (Table 3). Glycemic variability also increased over the course of the intervention, with higher change in the SD of the mean glucose measurements in the water arm than in the ASB arm (2.6; SE 1.7; P = 0.13).

Per-Protocol and Sensitivity Analyses

The results from per-protocol and sensitivity analyses were all consistent with the

Table 1—Baseline participant characteristics in SODAS

Characteristic	Total (*N* = 181)	ASB (*n* = 91)	Water (*n* = 90)
State			
California	90	46	44
Minnesota	91	45	46
Sex			
Female	94	47	47
Male	87	44	43
Age (years)	60.1 (10.2)	59.6 (10.4)	60.7(10.1)
Race			
African American or Black	6	4	2
Hispanic/Latino/Latina	20	9	11
White (non-Hispanic)	135	68	67
Other (non-Hispanic)*	20	10	10
Education			
College or above	117	59	58
High school/some college	64	32	32
Duration of diabetes (years)	11.9 (8.3)	10.1 (7.4)	13.7 (8.7)
HbA_{1c} %	7.19 (0.9)	7.19 (1.1)	7.20 (0.7)
MES	1.77 (1.28)	1.60 (1.06)	1.97 (1.45)
Uses insulin (*n*)	54	25	29
Modified therapeutic intensity score (blood pressure)†	0.39 (0.47)	0.39 (0.51)	0.39 (0.43)
Lipid (statin) therapy intensity‡			
None	49	30	19
Low	9	1	8
Moderate	81	37	44
High	42	23	19
BMI (kg/m^2)	34.3 (7.0)	35.3 (7.1)	33.2 (6.7)
Usual ASB daily intake (oz/day)	22.5 (17.6)	21.4 (15.6)	23.6 (19.5)
Duration (years) of ASB intake	26.8 (14.6)	26.7 (15.3)	27.0 (14.0)
Usual commercial ASB composition			
Aspartame/Ace-K	138	69	69
Aspartame/Ace-K/sucralose	35	17	18
Stevia	4	3	1
Sucralose	4	2	2

Data are reported as mean (SD) unless otherwise indicated. Ace-K, acesulfame potassium. *Other (non-Hispanic) includes South and Southeast Asian, East Asian (Korean, Chinese, Japanese), Native Hawaiian/Pacific Islander, American Indian or Alaskan Native, or identified with multiple racial or ethnic groups. Because of small numbers, these groups are presented as a collated group to avoid potentially identifying participants. †The modified therapeutic intensity score is a validated summary measure that accounts for the number of antihypertensive medications in a participant's regimen and the dose of each medication the participant is receiving relative to the Food and Drug Administration maximally recommended dose modified for the 2017 American College of Cardiology/American Heart Association blood pressure guideline–defined maximum dose for each agent. ‡2018 American Heart Association/American College of Cardiology Guideline on the Management of Blood Cholesterol classification of therapeutic intensity (20).

main results (Supplementary Table 1). Specifically, adjustment for duration of type 2 diabetes, caffeine intake, class of usual artificial sweetener intake via ASBs, COVID-19 infection, and exclusion of insulin use did not materially alter the findings for the primary outcome. Sex-stratified analyses were directionally consistent, with a greater magnitude of effect in female participants.

CONCLUSIONS

This randomized dietary intervention in people with T2D tested the underlying hypothesis informing the general guidance from standard of care and medical nutritional therapy guidelines related to ASB intake in people with T2D. The findings suggest substituting water for ASBs by people with T2D who regularly consume ASBs does not improve any clinical measures related to glycemia or weight over 24 weeks. In fact, the participants randomized to consume water in place of habitual ASB intake had a clinically and statistically significant increase in HbA_{1c} over 24 weeks compared with participants who maintained habitual intake of ASBs, contrary to the hypothesis. Related measures from CGM metrics provide context for underlying glycemic dynamics during the intervention: percent TIR declined at a clinically significant effect size (>3%) (but a nonstatistically significant level) over the course of the intervention in the water arm relative to the ASB arm, and glycemic variability and time above range were increased as well. There was also a statistically significant difference in mean level of weight change in the water arm compared

Table 2—Summary statistics and effect estimates over 24 weeks of substituting water for ASBs for primary and secondary clinical glycemic and weight outcomes in people with T2D

	ASB (n = 91)			Water (n = 90)			Mean difference in change from baseline-24 week (water − ASB)		
	n	Mean	SD	n	Mean	SD	Estimate*	SE	P value
Primary outcome									
HbA_{1c} (%)									
Baseline	91	7.19	1.10	90	7.20	0.69			
12 weeks	86	7.13	1.02	84	7.43	1.02			
24 weeks	91	7.14	1.19	87	7.44	1.04	0.29	0.12	0.013
Secondary outcome									
Fructosamine (μmol/L)									
Baseline	90	273.2	44.8	88	285.5	42.4			
12 weeks	85	272.1	43.5	82	286.6	47.2			
24 weeks	90	273.0	51.3	88	291.6	45.8	6.22	4.92	0.21
Fasting glucose (mg/dL)									
Baseline	90	147.5	40.0	88	147.6	36.2			
12 weeks	85	146.2	41.8	83	149.3	44.2			
24 weeks	90	149.2	44.0	87	153.7	51.3	4.71	6.43	0.47
Fasting insulin (pmol/L)									
Baseline	89	128.0	97.1	88	138.5	134.1			
12 weeks	84	135.7	141.0	81	134.2	145.0			
24 weeks	89	143.5	145.4	86	144.2	144.2	−11.8	13.4	0.38
Weight (kg)									
Baseline	91	102.1	21.1	90	96.1	21.5			
12 weeks	91	101.5	20.4	88	95.8	21.8			
24 weeks	90	101.2	20.6	88	95.9	21.9	1.11	0.55	0.045

Summary statistics are unadjusted means and SD. *Model estimate adjusted for sex, study site, and MES.

with the ASB arm, but the level is not considered clinically significant (∼1%) (21). The primary outcome findings were consistent in per-protocol and a priori sensitivity analyses, suggesting that the findings were robust to different statistical and analytic assumptions.

There is little evidence to compare with the SODAS results. In a study of 81 adult women (age <50 years) with obesity and T2D (HbA_{1c} <7.2%), only using metformin for diabetes control, and who were usual consumers of ASBs, all participants were part of a 24-week behavioral weight loss intervention, and half were randomized to consume water in place of ASB with lunch. In the secondary glycemic outcomes, there was clinically nonsignificant improvement in HbA_{1c} in the water arm compared with the ASB arm, and statistically significant improvements in fasting glucose and insulin levels and indices of insulin resistance in the water arm compared with the ASB arm (22). Similar results were reported in a 12-week randomized intervention of young adults with overweight and obesity who did not have T2D and who were usual consumers of ASBs. Participants substituting water for ASB had improved glycemic and metabolic measures relative to maintaining ASB intake (23). Although these two studies both focused on regular consumers of ASB, one study included participants at high risk for T2D (but did not have T2D), and the other study included participants with a specific T2D pharmaceutical regimen integrated into a weight loss study, limiting any direct comparisons to the SODAS.

The SODAS was a rigorously conducted, randomized, equicaloric dietary intervention with design and conduct elements that strengthen the inference of the results, despite the results being contrary to the hypothesis and not supporting current medical nutritional therapy and dietary recommendations for people with T2D. The pragmatic design used commercial ASBs consumed, because they are in the real world, to enhance adherence and generalizability of the intervention. Indeed, participants reported ideal levels of adherence to the intervention, but there is no objective measure of adherence to report. ASB intake is a self-selected behavior and consumers tend to have little variation in the beverages they habitually consume (24). Furthermore, commercial ASBs sweetened with one uniform AS compose a negligible proportion of intake (16). Although the actual amount of AS is proprietary information, we characterized individual AS blends for secondary analyses to inform the interpretation of the main effects. Adjustment for the AS blend or type did not alter the primary outcome results, and the study was not designed or powered to detect an effect in individual sweeteners or blends, limiting inference beyond general ASB intake. The supporting data collected over the course of the study (i.e., gut microbiome and biological samples for metabolomics, as well as detailed dietary, physical activity, sleep, and quality of life data) will allow us to examine potential hypothesized biological and behavioral avenues that may contribute to explaining the reported results in the future.

Overall, the results of the SODAs has implications for clinical care and medical nutritional therapy guidelines for people with T2D who are like the study population. Specifically, there was no benefit to substituting water for ASBs by people with T2D who regularly consume ASBs. If anything, the results suggest maintaining usual ASB intake may be a tool to continue to help manage T2D if glycemic measures are controlled and stable. However, replication of these results should be attempted to determine the robustness of the findings, which are contrary to other related data informing the guidelines and

Table 3—Summary statistics and effect estimates over 24 weeks of substituting water for ASBs regarding CGM metrics in people with T2D

	ASB (n = 91)			Water (n = 90)			Mean difference in change from baseline to 24 weeks (water − ASB)		
Metric	n	Mean	SD	n	Mean	SD	Estimate*	SE	P value
Time in range (%) 70–180 mg/dL (3.9–10.0 mmol/L)									
Baseline	88	76	19.2	87	72.3	20.9			
12 weeks	84	75.2	22.6	86	66.9	26.2			
24 weeks	87	72.8	23.2	83	64.7	26.5	−3.6	3	0.29
Time below range (%) <70 mg/dL (<3.9 mmol/L)									
Baseline	88	3	7.5	87	2.3	4.9			
12 weeks	84	2.7	5.1	86	2.8	5.3			
24 weeks	87	2.7	5.1	83	3.6	10.3	1.5	1.3	0.26
Time above range (%) >180 mg/dL (>10.0 mmol/L)									
Baseline	88	21.4	19.5	87	25.2	21.5			
12 weeks	84	22.8	24.3	86	30.2	27.1			
24 weeks	87	24.7	25.1	83	31.7	28	2.8	3.4	0.42
Mean glucose (mg/dL)†									
Baseline	88	147.3	42.1	87	151.4	33.1			
12 weeks	84	149.4	46.4	86	161.2	50.5			
24 weeks	87	153.1	50.7	83	162.3	47.3	4.6	5.4	0.39
SD of mean glucose (mg/dL)‡									
Baseline	88	39.6	14.7	87	42	13.1			
12 weeks	84	40	12.9	86	44.9	15.4			
24 weeks	87	40.8	14.9	83	45.8	16.3	2.6	1.7	0.13

Summary statistics are unadjusted means and SD. *Model adjusted for sex, study site, and MES. †Mean glucose refers to a measure of the mean 24-h glucose concentration calculated across all recorded glucose readings during the wear period. ‡The SD of mean glucose values is a measure of dynamic glucose variability; SD is strongly correlated with mean glucose.

the hypothesis. Nonetheless, these results are generalizable to people with T2D and, given the uneven body of evidence on ASB intake, randomized interventions of similar design are merited in different populations to inform scientific, clinical, and public health recommendations on ASB intake.

Funding. This work was supported by the National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases (grant R01DK117028).

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported

Author Contributions. A.O.O. conceived, designed, and supervised the study; wrote the first draft of the manuscript, and critically revised the manuscript. J.C. and L.J. did the analyses and critically revised the manuscript and study documents. S.Ra., S.Ry., and N.R.M. coordinated and conducted the study and data management and critically revised the manuscript. A.E.B., E.S., and A.R. contributed to clinical aspects of design, clinical patient oversight during trial conduct, and critically revised the manuscript. M.A.P. contributed to study design, supervised a study site, critically revised the manuscript and study documents, and interpreted results. All authors approved the final version. A.O.O. attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. A.O.O. and L.J. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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